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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/781,894	02/20/2004	Louis S. Kucera	053665-5012	4211

9629 7590 08/17/2010

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EXAMINER	
ANDERSON, JAMES D	
ART UNIT	PAPER NUMBER
1614	
MAIL DATE	DELIVERY MODE
08/17/2010	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/781,894	KUCERA ET AL.	
	Examiner	Art Unit	
	JAMES D. ANDERSON	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 June 2010*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,6-8 and 39* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-2, 6-8, and 39* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Formal Matters

Applicants' response and amendments to the claims, filed 6/23/2010, are acknowledged and entered. Claims 1-2, 6-8, and 39 are pending and under examination.

Response to Arguments

Applicants' arguments, filed 6/23/2010, have been fully considered but they are not deemed to be persuasive. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

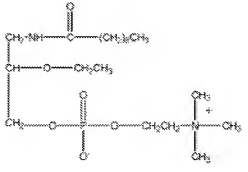
> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

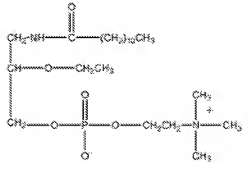
Claims 1-2, 6-8, and 39 are rejected under 35 U.S.C. 103(a) as being unpatentable over **Kucera *et al.*** (U.S. Patent No. 5,962,437; Issued Oct. 5, 1999; Filed Aug. 7, 1995) in view of **Kucera *et al.*** (U.S. Patent No. 5,770,584; Issued Jun. 23, 1998; Filed Jun. 6, 1995).

Claimed Invention

The instant claims recite methods of treating RSV infections comprising administering a compound having the formula



or



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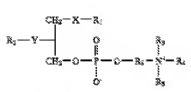
Teachings of Kucera et al. ('437)

Kucera *et al*. teach methods of treating viral infections comprising administering to a subject a phospholipid or phospholipid derivative (Abstract). Such phospholipid derivatives are defined as compounds of Formula I:



In the compounds of Formula I, R_1 is a branched or unbranched, saturated or unsaturated C_6 to C_{24} alkyl group optionally substituted from 1 to 5 times with —OH, —COOH, oxo, amine, or substituted or unsubstituted aromatic; X is selected from the group consisting of NHCO, CH_2NCO, CONH, $CONCH_3$, S, SO, SO_2, O, NH, and NCH_3; R_2 is a branched or unbranched, saturated or unsaturated C_6 to C_{24} alkyl group optionally substituted from 1 to 5 times with —OH, —COOH, oxo, amine, or substituted or unsubstituted aromatic; Y is selected from the group consisting of NHCO, CH_2NCO, CONH, $CONCH_3$, S, SO, SO_2, O, NH, and NCH_3; R_3 is a branched or unbranched C_2 to C_5 alkyl group; and R_3, R_4, and R_5 are independently methyl or ethyl, or R_3 and R_4 together form an aliphatic or heterocyclic ring having five or six members and R_5 is methyl or ethyl. Preferred compounds include 1-dodecanamido-2-decyloxypropyl-3-phosphocholine, 1-dodecanamido-2-octyloxypropyl-3-phosphocholine, and 1-dodecanamido-2-dodecyloxypropyl-3-phosphocholine. The method is particularly preferred as a treatment to combat viral infections caused by HIV-1, HBV, and herpes simplex virus. The present invention also includes pharmaceutical compositions comprising a compound of Formula I and a suitable pharmaceutical carrier.

The compounds are taught to work via attachment to cell membranes and thus are particularly effective against infections caused by membrane-containing or envelope-containing viruses (col. 9, lines 42-45). While Kucera *et al.* exemplify the treatment of HIV-1 infections, the inventors state that the compounds of Formula I can also be used to treat the instantly claimed respiratory syncytial virus infections (col. 9, lines 56-61). With respect to claim 39, which recites modes of administration, Kucera *et al.* teach the same modes of administration (col. 10, lines 14-21).

The presently amended claims differ from Kucera *et al.* in that the claimed compounds are now limited to compounds wherein R_1 is -NHC(O)C_{11} alkyl; R_2 is –OX, where X is ethyl; and R_3 is phosphocholine. In the compounds disclosed in Kucera *et al.*, X-R_1 corresponds to the claimed -NHC(O)C_{11} alkyl substituent; –Y-R_2, wherein Y is O and R_2 is a branched or unbranched, saturated or unsaturated C_6 to C_{14} alkyl group corresponds to the $-OCH_2CH_3$ substituent; and when R_6 is ethyl and R_3, R_4, and R_5 are methyl corresponds to the claimed phosphocoline. The instantly claimed compounds thus differ from the genus of compounds disclosed in Kucera only in the length of the R_2 alkyl chain. Whereas Kucera *et al.* disclose that

the R_2 alkyl chain can be from C_6 to C_{14} alkyl group, the instantly claimed compounds comprise a C_2 alkyl group.

Kucera *et al.* clearly suggest that the length of attached alkyl groups can be modified and still elicit functional antiviral compounds. For examples, compounds wherein R_2 is C_8, C_{10}, and C_{12} were all demonstrated to have antiviral activity (Table 1). The courts have held that "structural similarity between claimed and prior art subject matter, proved by combining references or otherwise, where the prior art gives reason or motivation to make the claimed compositions, creates a prima facie case of obviousness." *Dillon*, 919 F.2d at 692. In addition to structural similarity between the compounds, a prima facie case of obviousness also requires a showing of "adequate support in the prior art" for the change in structure. *In re Grabiak*, 769 F.2d 729, 731-32 [226 USPQ 870] (Fed. Cir. 1985).

The court elaborated on this requirement in the case of *In re Deuel*, 51 F.3d 1552, 1558 [34 USPQ2d 1210] (Fed. Cir. 1995), where the court stated that "[n]ormally a prima facie case of obviousness is based upon structural similarity, *i.e.*, an established structural relationship between a prior art compound and the claimed compound." That is so because close or established "[s]tructural relationships may provide the requisite motivation or suggestion to modify known compounds to obtain new compounds." *Id.* A known compound may suggest its homolog, analog, or isomer because such compounds "often have similar properties and therefore chemists of ordinary skill would ordinarily contemplate making them to try to obtain compounds with improved properties." *Id.*

In the instant case, Applicant's compounds differ from Kucera's compounds in that the claimed compounds are merely homologs of those disclosed in Kucera (*i.e.*, the claimed compounds only differ in the length of the alkyl chain attached at the R_2 position of the Kucera compounds. Kucera discloses branched or unbranched, saturated or unsaturated C_6 to C_{14} alkyl groups whereas the instantly claimed compounds comprise a C_2 alkyl group. However, in light of the fact that Kucera clearly contemplates that the alkyl groups attached to the R_2 position can vary greatly (from C_6 to C_{14} carbons) and further in view of the fact that compounds with differing alkyl chain lengths all possess antiviral activity, one skilled in the art would have found

it obvious that a compound having chain length of C_2 carbons would also possess antiviral activity.

Teachings of Kucera et al. ('584)

In support of the above findings, the Examiner additionally cites Kucera *et al.* ('584) who disclose methods of treating hepatitis virus infections comprising administering compounds of Formula I, which compounds are structurally related to the claimed compounds and those disclosed in Kucera *et al.* ('437) (see col. 1, line 60 to col. 2, line 48). See also compounds CP-49 and CP-51 in Example 6, which are phospholipid compounds as recited in the instant claims wherein R_2 -CH_2CH_3. These compounds were demonstrated to have anti-HBV activity. Compare to Kucera *et al.* ('437), wherein compound CP-128 (R_2 is C_{10}) disclosed therein is also demonstrated to have anti-HBV activity (Example 9).

Principles of Law

The question of obviousness is resolved on the basis of underlying factual determinations including: (1) the scope and content of the prior art; (2) the level of ordinary skill in the art; (3) the differences between the claimed invention and the prior art; and (4) secondary considerations of nonobviousness, if any. *Graham v. John Deere Co.*, 383 U.S. 1, 17 (1966). The Supreme Court has emphasized that "the [obviousness] analysis need not seek out precise teachings directed to the specific subject matter of the challenged claim, for a court can take account of the inferences and creative steps that a person of ordinary skill in the art would employ." *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 418 (2007).

Analysis & Examiner's Determination of Obviousness

It would have been *prima facie* obvious to one of ordinary skill in the art at the time of Applicant's invention to use the compounds of the two formulas as recited in the instant claims for the treatment of respiratory syncytial virus (RSV).

The prior art recognizes that phospholipid derivatives structurally related to the claimed compounds are useful in the treatment of viral infections, including hepatitis B and RSV.

Specifically, Kucera et al. ('437) teaches that phospholipid derivatives structurally related to the claimed compounds are effective in the treatment of hepatitis B infections and suggest that the phospholipid derivatives disclosed therein are also useful in treating RSV infections. Kucera et al. ('584) teaches that phospholipid derivatives structurally related to those disclosed in Kucera et al. ('437) and structurally related to the claimed compounds are also effective in the treatment of hepatitis B infections.

Thus, both Kucera et al. ('437) and Kucera et al. ('584) teach that phospholipid derivatives structurally related to the claimed compounds are useful in the treatment of viral infections such as RSV. As such, the skilled artisan would have recognized that modifications of the alkyl chain length (*e.g.*, shortening or lengthening) in the compounds disclosed in both Kucera et al. references would lead to compounds also having activity in the treatment of viral infections.

Accordingly, the instantly claimed methods of treating RSV infections comprising administering a compound having the formulas recited in the instant claims would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made. Kucera *et al.* ('437) clearly motivate one skilled in the art to use phospholipid derivatives having the same core structure as those recited in the instant claims to treat viral infections and even teach that respiratory syncytial virus infections are a type of infection that may be treated with the compounds of the invention. Kucera *et al.* ('584) is provided as evidence that compounds having lower alkyl groups in the R_2 position maintain antiviral activity. As such, one skilled in the art would have been imbued with at least a reasonable expectation that the compounds of Formula I as taught in Kucera *et al.* ('437) having a C_2 alkyl group in the R_2 position would also be effective at treating viral infections, including the instantly claimed RSV, as evidenced by Kucera *et al.* ('584).

Response to Arguments

Applicants' arguments have been carefully considered but they are not deemed persuasive.

Applicants argue that the basis for the activity of the compounds of Formula (I) of Kucera '437 is that the compounds are considered analogs of phosphatidylcholine with lipophilic moieties represented by R_1 and R_2, wherein R_2 in particular is preferably a C_8-C_{12} alkyl group, and even more preferably a C_8 or a C_{10} alkyl group. Kucera '437 broadly teaches that R_2 is a "branched or unbranched, saturated or unsaturated **C_6 to C_{14} alkyl group** (col. 2, lines 19-20; col. 5, lines 60-61). The teachings of Kucera '437 are not limited by the preferable embodiments disclosed therein.

Applicants argue that since a chain of 8 or 10 carbon atoms is described as preferred for R_2, it would not be an obvious modification of R_2 to replace the 8- or 10-carbon chain with a 2-carbon chain with no rationale for doing so. In response, the Examiner respectfully submits that the rationale for doing so is provided in the teachings of Kucera ('584). In this regard, Kucera '584 also teaches phosphatidylcholine derivatives for the treatment of viral infections, wherein in substituent X, which corresponds to substituent Y-R_2 in the compounds of Kucera ('437), can be a covalent bond or methylene optionally substituted with hydroxyl, C_1-C_{20} alkyl, **C_1-C_{20} alkoxy**, C_1-C_{20} alkylthio, or C_1-C_{20} alkylamido (col. 2, lines 1-12). More specifically, Kucera ('584) teaches "alkyl lipids" CP-49 and CP-51 in Example 6, which are phospholipid compounds as recited in the instant claims wherein R_2 -CH_2CH_3 and are demonstrated to have anti-HBV activity. As such, it is clear from the combined teachings of Kucera ('437) and Kucera ('584) that the R_2 substituent in the compounds of Kucera ('437) allows for lower alkyl groups while maintaining anti-viral activity.

Applicants argue that R_1 is described in Kucera '584 as being C_{14}-C_{18}, which is "well outside the values of C_9 and C_{11} respectively recited for R_1 for the two compounds of Applicants' claim 1". As a first matter, C_{14}-C_{18} is not "well outside" C_9 and C_{11} as asserted by Applicants. The difference between Applicants' claimed alkyl chain and that of Kucera '584 is only 3-9 carbon atoms. Further, Kucera '437 teaches that compounds wherein R_1 is **C_6 to C_{18} alkyl group** have anti-viral activity.

Pertinent to the present rejection, the following compounds were tested for anti-HBV activity by Kucera ('437) and Kucera ('584):

Compound	R_1	R_2	R_3
CP-128 (Kucera '437)	$NHC(O)C_{11}H_{23}$	$C_{10}H_{21}$	PC
CP-130 (Kucera '437)	$NHC(O)C_{11}H_{23}$	C_8H_{17}	PC
CP-131 (Kucera ('437)	$NHC(O)C_{11}H_{23}$	$C_{12}H_{25}$	PC
CP-48 (Kucera '584)	$NHC(O)C_{15}H_{31}$	CH_3	PC
CP-49 (Kucera '584)	$NHC(O)C_{15}H_{31}$	CH_2CH_3	PC
CP-51 (Kucera '584)	$NHC(O)C_{17}H_{35}$	CH_2CH_3	PC

PC = phosphocholine [$OPO_3CH_2CH_2N^+(CH_3)_3$]

All of the above compounds were found to have anti-HBV activity *in vitro*. It is clear from the testing of these compounds that the R_2 substituent has little effect on the biological activity of the compounds disclosed in the Kucera references. Compounds ranging from C_1 to C_{12} carbon atoms in the R_2 position all have antiviral activity as evidenced by the Kucera references. As such, the Examiner is not persuaded that by Applicants' arguments that it would not be obvious to formulate compounds of the Kucera references wherein R_1 is $NHC(O)C_9H_{19}$ and R_2 is CH_2CH_3 or wherein R_1 is $C_{11}H_{23}$ and R_2 is CH_2CH_3 as recited in the instant claims. Based on the anti-HBV activity of the compounds tested in the Kucera references, one skilled in the art would reasonably expect the claimed compounds to also have anti-viral activity as suggested by the teachings of the Kucera references.

Applicants argue that if one skilled in the art found the motivation to modify the R_2 region of the compounds of Kucera '437 so as to make R_2 significantly less lipophilic based on the teachings of Kucera '584, then that same person would be equally motivated to increase the minimum number of carbon atoms in the R_1 region of the Kucera '437 compounds from 6 to a minimum of 14 carbon atoms as described in Kucera '584. This argument is not found persuasive because as clearly demonstrated in Kucera '584, compounds wherein R_2 is methyl or ethyl and wherein R_1 has 15 or 17 carbon atoms maintain anti-viral activity. Applicants have presented no factual evidence that having 9 or 11 carbon atoms in the R_1 position possess anti-viral activity that would not be expected based on the teachings of the Kucera references. In fact, Applicants have presented no factual evidence that there exist compounds encompassed by the teachings of the Kucera references that do **not** have anti-viral activity. In contrast, the

Examiner has provided factual evidence that compounds of the Kucera references having 11 to 17 carbon atoms in the R_1 position and 1 to 12 carbon atoms in the R_2 position all possess anti-viral activity.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to JAMES D. ANDERSON whose telephone number is (571)272-9038. The examiner can normally be reached on MON-FRI 9:00 am - 5:00 pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel can be reached on 571-272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/James D. Anderson/

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